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Total synthesis of pederin, a potent insect toxin: the efficient synthesis of the right half, (+)-benzoylpedamide

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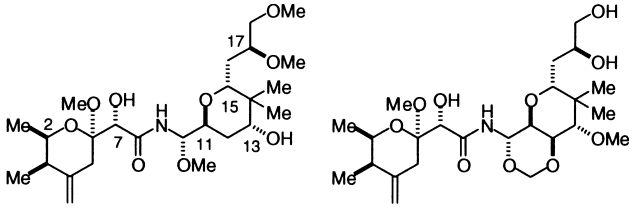
Abstract—A simple and efficient synthesis of (+)-benzoylpedamide, the right half of pederin, was achieved in 16 steps with a 35% overall yield from (*S*)-malic acid. The key steps include the SmI_2-mediated intramolecular Reformatsky reaction, stereoselective allylation, the Sharpless asymmetric dihydroxylation, and amidation. The total synthesis of pederin was accomplished via coupling of the left and right halves. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

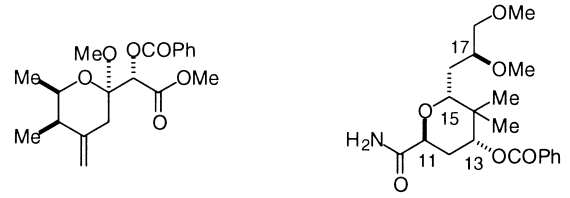
Pederin (**1**), a potent insect toxin isolated from *Paederus fuscipes*, is the first member of the pederin family (Fig. 1). In 1968, the absolute and relative structure of **1** was determined by X-ray crystallographic analysis.[1] The unique structure bearing two tetrahydropyran rings bridged by an *N*-acyl aminal remained as only one example in the realm of natural products until 1988 when mycalamide A (**2**)[2a] and onnamide A[3a] were isolated from New Zealand and Japanese marine sponges, respectively. At the present, this family grew to a large family that included pederin, mycalamides A and B,[2] onnamides A–F,[3] and theopederins A–L.[4] All of these natural compounds contain an identical left half, but slightly different right halves. Many members of this family exhibit remarkable biological acitivity as antitumour and antiviral agents. Pederin (**1**) inhibits mitosis in HeLa cells and blocks protein and DNA biosynthesis.[5] Mycalamide A (**2**) exhibits in vivo potent antitumor and antiviral activity, and immunosuppressive action via inhibition of T-cell activation, which is 10-fold more potent than FK-506.[6]



Pederin (**1**) Mycalamide A (**2**)

Figure 1.

Their unique structure and potent biological activity have attracted the attention of numerous synthetic organic chemists. The total syntheses have been reported for pederin,[7–9] mycalamides A[10,11] and B,[9,12] onnamide A,[13] and theopederin D.[14] However, a more efficient method for the synthesis of the left and right halves is still required. Recently, we reported a substantially improved, short and highly efficient synthesis of (+)-methyl benzoylpederate (**3**) (Fig. 2), the identical left half of the pederin family, in nine steps with a 23% overall yield from the Evans chiral amide.[15] Our attention then turned to the efficient synthesis of the right halves of this family. We herein describe a simple and highly efficient synthesis of (+)-benzoylpedamide (**4**), the right half of pederin (**1**), and the total synthesis of **1**.



(+)-Methyl benzoylpederate (**3**) (+)-Benzoylpedamide (**4**)

Figure 2.

Keywords: samarium diiodide; Reformatsky reaction; Sharpless asymmetric dihydroxylation; allylation.

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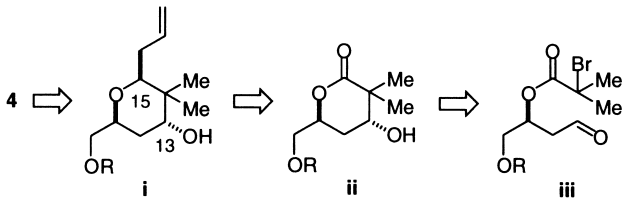
2. Results and discussion

2.1. Synthetic plan

Our synthetic strategy for (+)-benzoylpedamide (**4**) is outlined in Scheme 1. The C15 side chain of **4** would be constructed from δ-lactone **ii** via **i** by stereoselective allylation and dihydroxylation. The key intermediate **ii** should be synthesized by the C13–C14 bond formation. We anticipated that this cyclization could be stereoselectively performed by the SmI_2-mediated intramolecular Reformatsky reaction[16] of 2-bromoisobutyrate and aldehyde in **iii**. The 2-bromoisobutyrate **iii** will be prepared from the commercially available (*S*)-malic acid.



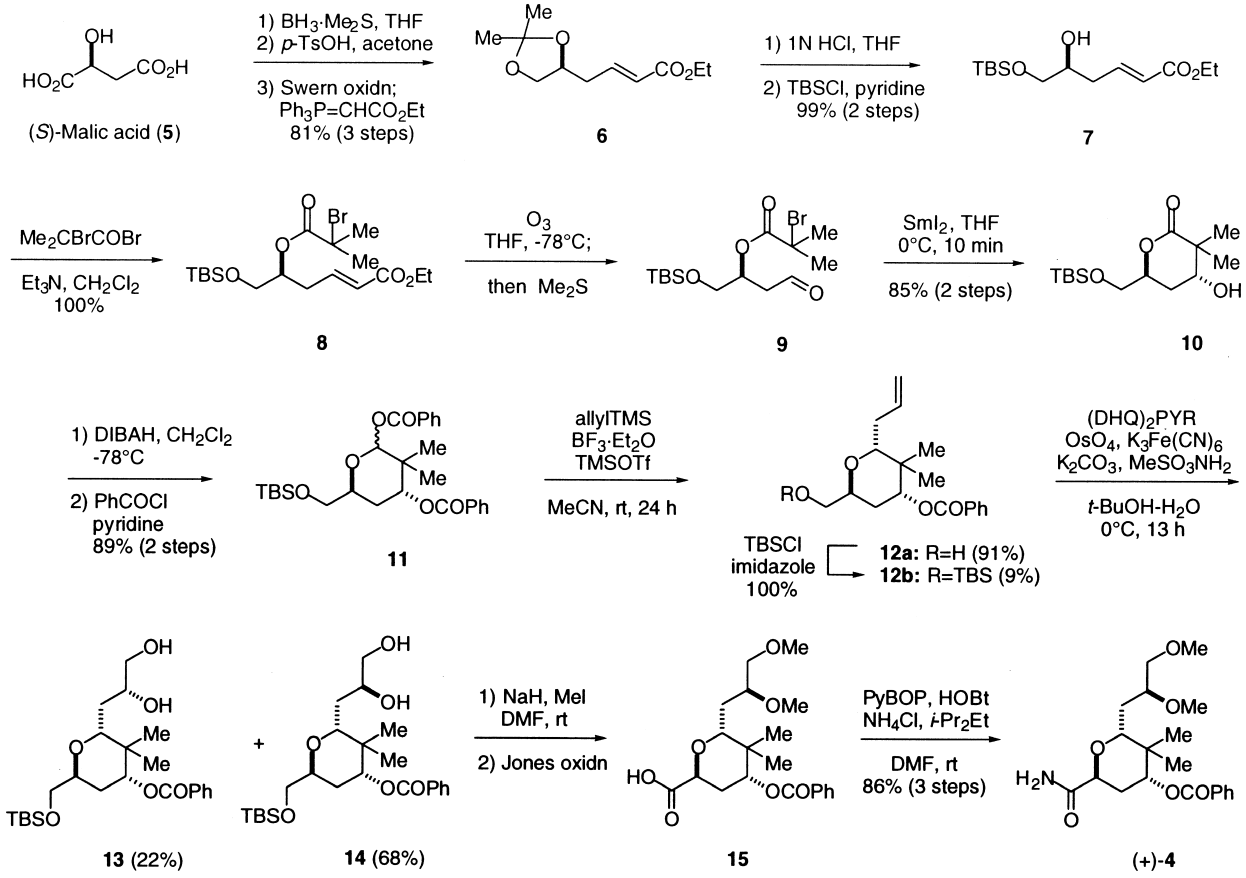
Scheme 1.

2.2. Synthesis of (+)-benzoylpedamide (4)

(*S*)-Malic acid (**5**) was first converted into the δ-hydroxy α,β-unsaturated ester **7** by a modification of a published procedure (Scheme 2).[17] The hydroboration of **5** followed by acetonization gave 1,2-*O*-isopropylidene-(*S*)-butane-1,2,4-triol in 91% yield, which was subjected to the one-pot Swern oxidation–Wittig reaction to give the α,β-unsaturated ester **6** in 89% yield. Deprotection of the acetonide in **6** under acidic conditions followed by monosilylation with TBSCl afforded the TBS ether **7** in 99% yield.

The alcohol **7** was then converted into the aldehyde **9**, which is the substrate for the SmI_2-mediated Reformatsky reaction, a key reaction in this synthesis. The acylation of **7** with 2-bromoisobutyryl bromide in CH_2Cl_2 in the presence of Et_3N quantitatively afforded 2-bromoisobutyrate **8**. Oxidative cleavage of the double bond in **8** by ozonolysis gave the required aldehyde **9**. The treatment of **9** with 3 equiv. of SmI_2 in THF at 0°C effected the reductive cyclization to give the δ-lactone **10** as a single product in 85% yield (from **8**). The ^1H NMR analysis suggested that the product **10** has the desired *axial* hydroxyl group. The present reaction would stereoselectively proceed through a tight cyclic transition state by chelation of the Sm(III) ester enolate and aldehyde as shown in Fig. 3.[16] Thus, the SmI_2-mediated intramolecular Reformatsky reaction efficiently took place with complete stereoselection even in the sterically hindered bromoester.

The introduction of the C15 side chain was then examined by allylation to the lactol derivative and stereoselective dihydroxylation to the olefin. The reduction of the lactone **10** with DIBAH gave the lactol, which was treated with



Scheme 2.

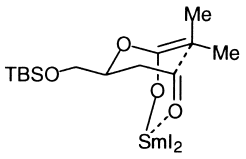


Figure 3.

PhCOCl to give the dibenzoate **11** in 89% yield as a 2.2:1 anomeric mixture. The treatment of **11** with 5 equiv. of allyltrimethylsilane in the presence of $BF_3{\cdot}Et_2O$ (0.2 equiv.) and TMSOTf (0.2 equiv.) in MeCN at room temperature effected the allylation with complete *axial* stereoselectivity.[18] The products were the alcohol **12a** (91%) and TBS ether **12b** (9%). The alcohol **12a** was quantitatively converted to the TBS ether **12b** by treatment with TBSCl. Dihydroxylation of the double bond in **12b** was then carried out by the Sharpless asymmetric dihydroxylation (AD).[19] After several attempts, we chose $(DHQ)_2PYR$ as the ligand, which generally gives good results for monosubstituted terminal olefins.[20] The treatment of **12b** under conditions using $(DHQ)_2PYR$, $K_3Fe(CN)_6$, K_2CO_3, OsO_4, and $MeSO_3NH_2$ in *t*-BuOH–H_2O provided the desired (17*S*)-alcohol **14** (68%) and its (17*R*)-epimer **13** (22%).

The remaining tasks for the synthesis of (+)-benzoylpedamide (**4**) are the formation of the C17,18-dimethoxy and C11-amide functions. After dimethylation of the diol **14** with NaH and MeI, treatment with Jones reagent effected desilylation and oxidation to give the carboxylic acid **15**. Finally, amidation was performed by the procedure[21] using PyBOP, HOBT, and NH_4Cl to give the amide **4** in 86% yield from **14**. The spectral data (^1H, ^{13}C NMR, and $[\alpha]_D$) and mp of **4** were identical with those of the authentic sample,[8] previously prepared by this group. Thus, the efficient synthesis of (+)-benzoylpedamide (**4**), the right half of pederin, was performed in 16 steps with a 35% overall yield from (*S*)-malic acid (**5**).

2.3. Total synthesis of pederin (1)

Having completed the synthesis of the right half **4**, we carried out its union with the left half **3**, prepared by our efficient procedure,[15] to give pederin (**1**) (Scheme 3). Coupling of both segments **3** and **4** was performed in a manner similar to that reported by Matsumoto et al.[7]

Hydrolysis of the methyl ester **3** with *n*-PrSLi in HMPA followed by treatment with $SOCl_2$ afforded the acid chloride **16**. Another coupling partner **17**, methyl pedimidate, was prepared by treatment of **4** with $Me_3O^+BF_4^-$. The coupling of **16** and **17** in the presence of Et_3N gave *N*-acylimidate, which was immediately reduced with $NaBH_4$ in EtOH to give a separable 1:3 mixture of (+)-dibenzoylpederin (**18**) and the C10-epimer **19** in 36% overall yield from **4**. The spectral data of the dibenzoate **18** were identical with those of the authentic (+)-dibenzoylpederin.[7,8] Completion of the total synthesis of pederin (**1**) has already been performed by the hydrolysis of **18** with 1N LiOH in MeOH.[7]

3. Conclusion

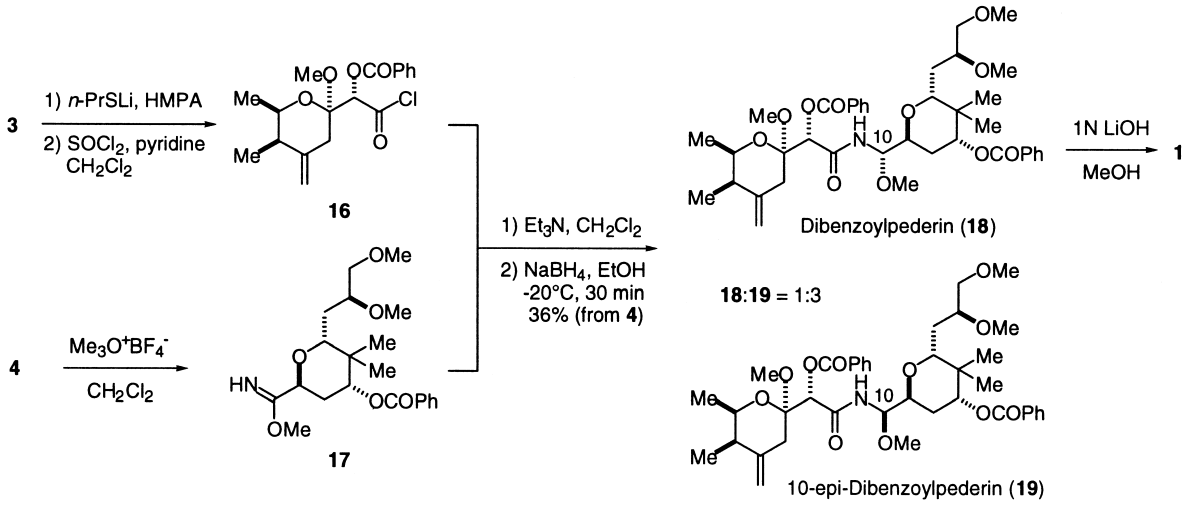
We have developed a simple and efficient method for the synthesis of (+)-benzoylpedamide (**4**), the right half of pederin (**1**). The total synthesis of pederin (**1**) was accomplished via coupling of the right and left halves. Further studies on the efficient synthesis of the right halves of mycalamides and theopederins based on the present method are now in progress in this laboratory.

4. Experimental

4.1. General

Flash column chromatography was performed using Kanto silica gel 60N (spherical, neutral; 40–100 μm). Melting points were determined using a Yanaco MP-500 apparatus and are uncorrected. Optical rotations were measured using a JASCO DIP-370 digital polarimeter. Infrared spectra were recorded using a JASCO VALOR-III FT-IR spectrometer. Mass spectra were measured using a JEOL AX-505. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-AL and a JEOL JNM-ECP.

4.1.1. α,β-Unsaturated ester 7. To a stirred solution of **6**



Scheme 3.

(408.4 mg, 1.91 mmol) in THF (7.6 mL) was added 1N HCl (5.0 mL) at room temperature. After stirring for 23 h, NaCl (7.6 g) and EtOAc were added. The organic layer was washed with brine and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo (10°C) to give diol (332.2 mg, 1.91 mmol) as a yellow oil. To a stirred solution of the diol in pyridine (6.6 mL) was added TBSCl (373.6 mg, 2.48 mmol) at 0°C under an argon atmosphere. After stirring at room temperature for 17 h, saturated aqueous NH_4Cl was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2; *n*-hexane/EtOAc, 10:1, 5:1) to give **7** (544.6 mg, 99%) as a colorless oil. $[\alpha]_D^{27}=-1.2$ (*c* 1.11, $CHCl_3$); IR (neat) 3468, 1720, 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.98 (dt, *J*=15.6, 7.2 Hz, 1H), 5.90 (dt, *J*=15.6, 1.5 Hz, 1H), 4.18 (q, *J*=7.2 Hz, 2H), 3.79 (m, 1H), 3.64 (dd, *J*=10.1, 3.9 Hz, 1H), 3.45 (dd, *J*=9.9, 6.6 Hz, 1H), 2.37 (ddd, *J*=8.3, 6.8, 1.5 Hz, 2H), 1.28 (t, *J*=14.3, 7.2 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 144.7, 123.6, 70.5, 66.4, 60.2, 35.9, 25.8 (3×C), 18.2, 14.2, −5.47, −5.50. HRMS (FAB) calcd for $C_{14}H_{28}O_4SiNa$ ($M+Na^+$) 311.1655, found 311.1655.

4.1.2. 2-Bromoisobutyrate 8. To a solution of **7** (463.0 mg, 1.61 mmol) in CH_2Cl_2 (8.3 mL) were added Et_3N (477 μL, 3.21 mmol) and 2-bromoisobutyryl bromide (407 μL, 3.21 mmol) at 0°C under an argon atmosphere. After stirring at room temperature for 18 h, saturated aqueous NH_4Cl was added and the mixture was extracted with Et_2O. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2; *n*-hexane/EtOAc, 10:1) to give **8** (699.3 mg, 100%) as a yellow oil. $[\alpha]_D^{27}=-3.4$ (*c* 1.11, $CHCl_3$); IR (neat) 1736, 1716, 1659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (dt, *J*=15.2, 7.3 Hz, 1H), 5.90 (d, *J*=15.2 Hz, 1H), 4.98 (m, 1H), 4.18 (q, *J*=7.3 Hz, 2H), 3.70 (m, 2H), 2.60 (m, 2H), 2.00 (s, 3H), 1.91 (s, 3H), 1.28 (t, *J*=7.2 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 165.7, 143.0, 124.5, 74.2, 63.1, 60.3, 55.6, 33.1, 30.7 (2×C), 25.7 (3×C), 18.1, 14.2, −5.5 (2×C). HRMS (FAB) calcd for $C_{18}H_{33}O_5BrSiNa$ ($M+Na^+$) 461.1160, found 461.1182.

4.1.3. δ-Lactone 10. Ozone was bubbled to a stirred solution of **8** (791.1 mg, 1.81 mmol) in CH_2Cl_2 (15 mL) at −78°C for 20 min. After N_2 gas was bubbled to remove excess ozone, dimethyl sulfide (3.98 mL, 54.3 mmol) was added. After stirring at −78°C for 30 min, at 0°C for 1 h and at room temperature for 1 h, the yellow solution was concentrated in vacuo to give **9** as a yellow oil. To a stirred solution of **9** in THF (5.3 mL) was added SmI_2 (0.1 M in THF, 54.3 mL, 5.43 mmol) at 0°C under an argon atmosphere. After stirring at 0°C for 10 min, saturated aqueous NH_4Cl was added and the mixture was extracted with EtOAc. The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$–saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2; *n*-hexane/EtOAc, 3:1, 1:1) to give **10** (521.7 mg, 85%) as a colorless oil. $[\alpha]_D^{29}=-3.1$ (*c* 1.13, $CHCl_3$); IR (neat) 3447, 1733, 1713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.71 (ddt, *J*=11.0, 7.2, 3.9 Hz, 1H), 3.91 (br d, $W_{1/2}$=4.5 Hz, 1H), 3.89 (dd, *J*=11.0, 3.7 Hz, 1H), 3.68 (dd, *J*=11.0, 2.7 Hz, 1H), 2.38 (ddd, *J*=14.3, 11.0, 2.7 Hz, 1H), 2.05 (s, 1H), 1.83 (ddd, *J*=14.3, 4.5, 4.5 Hz, 1H), 1.34 (s, 3H), 1.28 (s, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 76.6, 72.0, 64.8, 43.2, 28.2, 25.8 (3×C), 22.0 (2×C), 18.2, −5.4, −5.6. HRMS (FAB) calcd for $C_{14}H_{28}O_4SiNa$ ($M+Na^+$) 311.1655, found 311.1655.

4.1.4. Dibenzoate 11. To a stirred solution of **10** (347.3 mg, 1.20 mmol) in CH_2Cl_2 (10 mL) was added DIBAH (1.0 M in hexane, 2.40 mL, 2.40 mmol) at −78°C under an argon atmosphere. After stirring at −78°C for 5 min, *i*-PrOH, EtOAc and saturated aqueous NH_4Cl were added. After stirring at room temperature for 40 min, the aqueous layer was extracted with EtOAc. The combined organic layers were washed with 1N HCl, dried over $MgSO_4$, and concentrated in vacuo to give lactol (322.4 mg, 1.11 mmol) as an oil. To a stirred solution of the lactol in pyridine (9.1 mL) was added PhCOCl (562 μL, 4.80 mmol) at 0°C under an argon atmosphere. After stirring at room temperature for 11 h, MeOH was added and the mixture was stirred for 40 min. The mixture was diluted with Et_2O, washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2; *n*-hexane/EtOAc, 15:1) to give **11** (532.6 mg, 89%, 2.2:1 anomeric mixture) as a colorless oil. IR (neat) 1739, 1733, 1717, 1602, 1586 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–8.10 (m, 10H), 6.20 (s, 0.69H), 6.14 (m, 0.31H), 5.27 (m, 0.69H), 5.24 (m,.0.31H), 4.30 (m, 0.31H), 4.14 (m, 0.69H), 3.72 (m, 1.38H), 3.69 (m, 0.62H), 2.19 (m, 0.31H), 2.10 (m, 0.69H), 1.85 (m, 1H), 1.56 (s, 3H), 1.31 (s, 0.94H), 1.30 (s, 2.06H), 0.85 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) major δ 165.3, 164.9, 133.2, 133.1, 129.8, 129.7, 129.6 (2×C), 129.4 (2×C), 128.4 (2×C), 128.3 (2×C), 96.3, 76.6, 73.1, 65.4, 37.9, 28.9, 25.9 (3×C), 20.9, 18.8, 15.3, −5.2, −5.3. Minor 166.0, 165.4, 132.9, 132.8, 130.3, 130.2, 129.9 (2×C), 129.5 (2×C), 128.2 (2×C), 128.1 (2×C), 97.5, 76.6, 73.9, 66.9, 36.6, 28.3, 25.9 (3×C), 21.2, 18.3, 15.3, −5.2, −5.3. HRMS (FAB) calcd for $C_{28}H_{38}O_6SiNa$ ($M+Na^+$) 521.2335, found 521.2359.

4.1.5. Allylation of 11. To a stirred solution of **11** (61.4 mg, 123.1 μmol) in MeCN (3 mL) were added $BF_3{\cdot}Et_2O$ (3.2 μL, 24.6 μmol), TMSOTf (4.6 μL, 24.6 μmol) and allyltrimethylsilane (98 μL, 615.6 μmol) at 0°C under an argon atmosphere. After stirring at room temperature for 24 h, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2; *n*-hexane/EtOAc, 10:1) to give **12a** (34.4 mg, 91%) and **12b** (4.9 mg, 9%) as colorless oils. **12a**: $[\alpha]_D^{29}=-0.55$ (*c* 1.09, $CHCl_3$); IR (neat) 3456, 1718, 1641, 1602, 1585 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (m, 2H), 7.59 (m, 1H), 7.47 (m, 2H), 5.91 (m, 1H), 5.14 (m, 2H), 5.05 (t, *J*=5.6 Hz, 1H), 4.11 (m, 1H), 3.82 (t, *J*=10.2 Hz, 1H), 3.51 (m, 2H), 2.61 (m, 1H), 2.34 (m, 1H), 2.04 (br, 1H), 1.90 (m, 2H), 1.09 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 136.1, 133.1, 130.2, 129.5 (2×C), 128.5

(2×C), 117.0, 78.3, 75.2, 69.1, 63.0, 37.4, 33.0, 27.7, 24.7 (2×C). HRMS (FAB) calcd for $C_{18}H_{24}O_4Na$ (M+Na^+) 327.1572, found 327.1578. **12b**: $[\alpha]_D^{26}$=+15.1 (*c* 1.15, $CHCl_3$); IR (neat) 1720, 1643, 1602, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (m, 2H), 7.58 (m, 1H), 7.46 (m, 2H), 5.95 (m, 1H), 5.15 (m, 2H), 5.05 (m, 1H), 4.00 (dt, *J*=10.5, 5.5 Hz, 1H), 3.79 (dd, *J*=10.5, 5.5 Hz, 1H), 3.71 (dd, *J*=10.5, 5.5 Hz, 1H), 3.58 (dd, *J*=10.5, 2.8 Hz, 1H), 2.53 (m, 1H), 2.29 (m, 1H), 1.93 (m, 2H), 1.05 (s, 3H), 1.04 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 136.7, 132.9, 130.5, 129.5 (2×C), 128.4 (2×C), 115.8, 79.0, 75.4, 70.1, 64.9, 37.5, 33.3, 28.1, 25.9 (3×C), 24.4 (2×C), 18.2, −5.4, −5.5. HRMS (FAB) calcd for $C_{24}H_{38}O_4SiNa$ (M+Na^+) 441.2437, found 441.2427.

4.1.6. TBS ether 12b from 12a. To a stirred solution of **12a** (117.4 mg, 0.39 mmol) in CH_2Cl_2 (4.8 mL) were added imidazole (92.1 mg, 1.35 mmol) and TBSCl (175.0 mg, 1.16 mmol) at 0°C under an argon atmosphere. After stirring at room temperature for 1.5 h, aqueous NH_4Cl was added and the mixture was extracted with Et_2O. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2; *n*-hexane/EtOAc, 10:1) to give **12b** (161.3 mg, 100%) as a colorless oil.

4.1.7. Sharpless AD of 12b. To a stirred suspension of $(DHQ)_2PYR$ (133.0 mg, 0.154 mmol) in *t*-BuOH–H_2O (1:1, 40 mL) were added K_2CO_3 (830.9 mg, 6.01 mmol), $K_3Fe(CN)_6$ (1.52 g, 4.62 mmol), OsO_4 (96.0 μL, 0.924 mmol) and $MeSO_3NH_2$ (184.7 mg, 1.69 mmol) at room temperature. After stirring at room temperature for 30 min, a solution of **12b** (644.7 mg, 1.54 mmol) in *t*-BuOH–H_2O (1:1, 8 mL) was added at 0°C. After stirring at room temperature for 13 h, Na_2SO_3 (2.2 g) was added at 0°C. After stirring at room temperature for 2 h, the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2; toluene/acetone, 7:1, 3:1) to give **13** (158.3 mg, 22%) and **14** (466.6 mg, 68%) as colorless oils. **13**: $[\alpha]_D^{29}$=+14.9 (*c* 1.20, $CHCl_3$); IR (neat) 3424, 1720, 1602, 1586 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (m, 2H), 7.56 (m, 1H), 7.42 (m, 2H), 5.01 (dd, *J*=10.1, 5.1 Hz, 1H), 4.07 (m, 2H), 3.97 (m, 1H), 3.78 (dd, *J*=11.2, 2.8 Hz, 1H), 3.62 (m, 1H), 3.55 (m, 2H), 3.17 (br, 2H), 1.53–1.93 (m, 4H), 1.07 (s, 3H), 0.93 (s, 3H), 0.90 (s, 9H), 0.09 (s, 6H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 132.9, 130.2, 129.4 (2×C), 128.4 (2×C), 75.2, 73.2, 71.5, 68.9, 66.5, 65.7, 37.7, 30.8, 27.5, 25.8 (3×C), 18.2, 15.1, 14.9, −5.4, −5.5. HRMS (FAB) calcd for $C_{24}H_{40}O_6SiNa$ (M+Na^+) 475.2492, found 475.2501. **14**: $[\alpha]_D^{29}$=+1.56 (*c* 1.11, $CHCl_3$); IR (neat) 3459, 1717, 1602, 1585 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (m, 2H), 7.59 (m, 1H), 7.46 (m, 2H), 5.08 (dd, *J*=8.0, 5.5 Hz, 1H), 4.15 (m, 1H), 3.92 (m, 2H), 3.79 (dd, *J*=11.0, 1.4 Hz, 1H), 3.63 (dd, *J*=11.0, 3.1 Hz, 2H), 3.52 (dd, *J*=11.0, 6.1 Hz, 1H), 2.36 (br, 1H), 1.98 (m, 1H), 1.89 (m, 2H), 1.62 (m, 1H), 1.07 (s, 3H), 1.01 (s, 3H), 0.93 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 133.0, 130.2, 129.5 (2×C), 128.4 (2×C), 79.2, 74.8, 72.5, 70.9, 66.6, 63.9, 37.7, 31.3, 27.5, 25.9 (3×C), 23.9 (2×C), 18.3, −5.50, −5.53. HRMS (FAB) calcd for $C_{24}H_{40}O_6SiNa$ (M+Na^+) 475.2492, found 475.2512.

4.1.8. Benzoylpedamide (4). To a stirred suspension of NaH (11.7 mg, 292.8 μmol) in DMF (0.5 mL) was added a solution of **14** (22.1 mg, 48.8 μmol) and MeI (15.2 μL, 243.8 μmol) in DMF (0.2 mL) at 0°C under an argon atmosphere. After stirring at room temperature for 4 h, 1N HCl–ice was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give dimethoxy compound as an oil. Jones reagent was added dropwise to a stirred solution of the product in acetone (0.51 mL) at 0°C until faint red color persisted. After stirring at room temperature for 30 min, the excess Jones reagent was destroyed by the addition of *i*-PrOH. The mixture was concentrated in vacuo, and then H_2O was added. The mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo to give **15** as an oil. The carboxylic acid **15**, PyBOP (60.2 mg, 115.2 μmol), and HOBt (15.5 mg, 115.2 μmol) were dissolved in DMF (0.3 mL) at 0°C under an argon atmosphere. To the mixture were added *i*-Pr_2NEt (44.7 μL, 307.2 μmol) and NH_4Cl (0.77 mg, 154.3 μmol) at room temperature. After stirring at room temperature for 1.5 h, H_2O and EtOAc were added and the mixture was extracted with EtOAc. The combined organic layers were washed with 1N HCl and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2; EtOAc) to give **4** (15.9 mg, 86%) as colorless crystals. mp 144–146°C (recrystallized from Et_2O–*n*-hexane); $[\alpha]_D^{26}$=+15.7 (*c* 3.26, $CHCl_3$); IR (KBr) 3432, 3330, 1719, 1684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (m, 2H), 7.54 (m, 1H), 7.45 (m, 2H), 5.49 (br. s, 2H), 4.98 (dd, *J*=10.7, 4.6 Hz, 1H), 4.48 (dd, *J*=6.6, 2.6 Hz, 1H), 3.61 (m, 2H), 3.55 (dd, *J*=8.7, 2.7 Hz, 1H), 3.45 (m, 1H), 3.42 (s, 3H), 3.39 (s, 3H), 2.59 (dd, *J*=13.1, 4.6, 2.7 Hz, 1H), 2.03 (ddd, *J*=13.1, 10.7, 6.6 Hz, 1H), 1.86 (m, 2H), 1.08 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 165.5, 133.0, 130.3, 129.6 (2×C), 128.4 (2×C), 78.9, 78.1, 74.9, 74.3, 72.4, 59.1, 56.6, 37.7, 30.1, 23.1, 14.4 (2×C). HRMS (FAB) calcd for $C_{20}H_{29}NO_6Na$ (M+Na^+) 402.1901, found 402.1891.

4.1.9. Dibenzoylpederin (18) and 10-*epi*-dibenzoylpederin (19). To a stirred solution of **4** (51.0 mg, 134.4 μmol) in CH_2Cl_2 (2.6 mL) was added $Me_3O^+BF_4^-$ (199.2 mg, 1.34 mmol) at 0°C under an argon atmosphere. After stirring at room temperature for 17 h, saturated aqueous $NaHCO_3$ and Et_2O were added at 0°C and the mixture was extracted with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$–brine, dried over $MgSO_4$, and concentrated in vacuo to give **17**. To a stirred solution of **3** (75.0 mg, 215.3 μmol) in HMPA (1.5 mL) was added *n*-PrSLi (0.55 M in HMPA, 585 μL, 236.8 μmol) at room temperature under an argon atmosphere. After stirring at room temperature for 6 h, ice was added and the mixture was extracted with Et_2O. To the aqueous layer were added 0.1N HCl (5 mL) and H_2O (5 mL) at 0°C and the mixture was extracted with Et_2O. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo to

give carboxylic acid. To a stirred solution of $SOCl_2$ (21.1 μL, 285.4 μmol) and pyridine (29.5 μL, 389.2 μmol) in CH_2Cl_2 (350 μL) was added dropwise a solution of carboxylic acid (69.4 mg, 207.6 μmol) in CH_2Cl_2 (430 μL) at room temperature under an argon atmosphere for 3 min. After stirring at room temperature for additional 2 min, a solution of **17** (55.3 mg, 140.5 μmol) and Et_3N (50.0 μL, 331.6 μmol) in CH_2Cl_2 (555 μL) was added. After stirring at room temperature for 2.5 h, the solvent was removed in vacuo. To the resulting residue was added at −20°C a suspension of $NaBH_4$ (128.9 mg, 3.32 mmol) in EtOH (3.25 mL) cooled at −20°C. After stirring at −20°C for 30 min, brine was added and the mixture was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2; *n*-hexane/EtOAc, 4:1, 3:1) to give **18** (8.53 mg, 9% from **4**) and **19** (25.6 mg, 27% from **4**) as colorless oils. **18**: $[\alpha]_D^{25}=+102.7$ (*c* 0.110, $CHCl_3$); IR (neat) 3428, 3366, 1723, 1655, 1603, 1586 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04–8.11 (m, 4H), 7.59 (m, 2H), 7.46 (m, 4H), 6.77 (d, *J*=9.6 Hz, 1H), 5.52 (s, 1H), 5.35 (dd, *J*=9.6, 4.1 Hz, 1H), 5.15 (dd, *J*=7.8, 4.1 Hz, 1H), 4.87 (s, 1H), 4.80 (s, 1H), 3.97 (m, 2H), 3.64 (dd, *J*=11.0, 1.8 Hz, 1H), 3.44–3.56 (m, 3H), 3.46 (s, 3H), 3.37 (s, 3H), 3.36 (s, 3H), 3.25 (s, 3H), 2.77 (d, *J*=14.2 Hz, 1H), 2.50 (d, *J*=14.2 Hz, 1H), 2.04–2.23 (m, 3H), 1.78–1.85 (m, 2H), 1.12 (d, *J*=6.4 Hz, 3H), 1.01 (s, 3H), 0.99 (s, 3H), 0.94 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 166.0, 165.4, 145.7, 133.5, 133.1, 130.1 (2×C), 129.5 (4×C), 128.5 (4×C), 110.5, 99.3, 81.7, 77.5, 77.3, 75.0, 72.8, 72.6, 70.2, 69.7, 59.2, 56.9, 56.4, 48.6, 41.3, 37.1, 34.1, 29.7, 29.1, 26.6, 24.7, 17.9, 11.9. HRMS (FAB) calcd for $C_{39}H_{53}O_{11}NNa$ ($M+Na^+$) 734.3445, found 734.3525. **19**: $[\alpha]_D^{26}=+126.5$ (*c* 0.170, $CHCl_3$); IR (neat) 3292, 1724, 1698, 1655, 1602 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06–8.11 (m, 4H), 7.85 (d, *J*=9.6 Hz, 1H), 7.57 (m, 2H), 7.44 (m, 4H), 5.41 (s, 1H), 5.35 (dd, *J*=8.3, 4.6 Hz, 1H), 5.19 (dd, *J*=9.6, 3.2 Hz, 1H), 4.88 (s, 1H), 4.81 (s, 1H), 4.00 (m, 2H), 3.82 (dd, *J*=11.5, 2.3 Hz, 1H), 3.75 (dd, *J*=10.1, 5.5 Hz, 1H), 3.69 (m, 1H), 3.49 (s, 3H), 3.48 (s, 3H), 3.45 (dd, *J*=10.1, 4.1 Hz, 1H), 3.37 (s, 3H), 3.26 (s, 3H), 3.09 (d, *J*=14.2 Hz, 1H), 2.50 (d, *J*=14.2 Hz, 1H), 2.26 (m, 1H), 2.14 (m, 1H), 2.04 (m, 1H), 1.90 (ddd, *J*=13.8, 8.3, 6.0, Hz, 1H), 1.83 (ddd, *J*=11.0, 8.7, 2.3, Hz, 1H), 1.19 (d, *J*=6.9 Hz, 3H), 1.05 (s, 3H), 1.04 (s, 3H), 1.02 (d, *J*=7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 166.0, 165.4, 146.3, 133.3, 133.0, 130.0 (2×C), 129.5 (4×C), 128.4 (2×C), 128.3 (2×C), 110.0, 99.7, 83.2, 78.1, 76.8, 75.3, 75.0, 72.2, 69.7, 69.6, 58.9, 56.9, 56.8, 48.2, 41.6, 37.2, 33.7, 29.7, 29.1, 27.7, 24.3, 17.9, 11.9. HRMS (FAB) calcd for $C_{39}H_{53}O_{11}NNa$ ($M+Na^+$) 734.3445, found 734.3525.

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